MAIL STOP APPEAL BRIEF-PATENTS
Attorney Docket No.: 27391U

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

BRUECK-SCHEFFLER		Conf. No.:	2887
Serial No.:	10/582,499	Art Unit:	1627
Filed:	June 9, 2006	Examiner:	CARTER, K.

For: **AQUEOUS SUSPENSIONS OF CICLESONIDE FOR NEBULISATION**

APPEAL BRIEF

This is an appeal to the Board of Patent Appeals and Interferences from the decision of Examiner Kendra Carter, mailed March 11, 2011, finally rejecting claims 1-10 and 12-20. Appellant timely filed a Notice of Appeal on June 8, 2011, making this Appeal Brief due by August 8, 2011. Accordingly, this paper is timely filed.

1. Table of Contents

2. The Real Party in Interest

The real party in interest in this appeal is NYCOMED GmbH.

3. Related Appeals and Interferences

Appellant is not aware of any other appeals or interferences that will directly affect, or be directly affected by, or have a bearing on the Board's decision in this appeal.

4. Status of Claims

The status of the claims is as follows upon filing of this Appeal Brief:

Claims cancelled: 11

Claims withdrawn from consideration but not cancelled: 21-41

Claims pending: 1-10 and 12-20

Claims objected to: None

Claims allowed: None

Claims rejected: 1-10 and 12-20

The claims on appeal are 1-10 and 12-20.

5. Status of Amendments

Appellant filed a Preliminary Amendment on June 9, 2006, in which claims 1-41 were amended.

Appellant filed an Amendment and Response on January 19, 2011, in which claims 1-2 were amended and claim 11 was canceled.

Along with a Notice of Appeal, appellant filed an Amendment and Response on June 8, 2011, in which claim 2 was amended to remove an objection to this claim.

No further amendments were made to the claims.

As such, appellant submits that claims 1-10 and 12-20 are the currently pending claims on appeal. The claims listed in the Claims Appendix herein incorporate the claim amendments of the aforementioned Amendment and Response.

6. Summary of Claimed Subject Matter

Independent claim 1 is directed to a method for preparing a sterile aqueous suspension of ciclesonide suitable for nebulization comprising the steps of:

a. providing an aqueous suspension of ciclesonide, containing at least one non-ionic agent for adjusting osmolality, and one or more pharmaceutically acceptable excipients, which one or more excipients are all non-ionic excipients; and

b. autoclaving the aqueous suspension provided in (a).

Basis for this claim is found in the specification on page 4, lines 17-22 and page 6, lines 1-9.

Independent claim 2 is directed to a method for preparing a sterile aqueous suspension of ciclesonide suitable for nebulization comprising the steps of:

a. providing an aqueous suspension of ciclesonide, containing at least one non-ionic agent for adjusting osmolality and optionally further one or more pharmaceutically acceptable excipients, which one or more excipients are all non-ionic excipients; and

b. autoclaving the aqueous suspension provided in (a).

Basis for this claim is found in the specification on page 4, lines 17-22 and page 6, lines 1-9.

7. Grounds of Rejection to be Reviewed on Appeal

A. Rejection of claims 1-4, 7-9 and 12-20 under 35 USC § 103(a)

Whether the identified claims are unpatentable under 35 USC § 103(a) as obvious over Nishibe (US 2006/0166953) in view of Saidi et al. (US 6,241,969) and Lintz et al. (US 2004/0247628).

B. Rejection of claim 5 under 35 USC § 103(a)

Whether the identified claim is unpatentable under 35 USC § 103(a) as obvious over Nishibe (US 2006/0166953) in view of Saidi et al. (US 6,241,969) and Lintz et al. (US 2004/0247628) and further in view of Allen et al. (J. Allergy Clin. Immunol., Sept. 2003, vol. 112, no. 3, pp. s7-s40) and ACS Registry (Feb. 1995, p. 1).

C. Rejection of claim 6 under 35 USC § 103(a)

Whether the identified claim is unpatentable under 35 USC § 103(a) as obvious over Nishibe (US 2006/0166953) in view of Saidi et al. (US 6,241,969) and Lintz et al. (US 2004/0247628) and further in view of Sambuco et al. (US 2005/0175546).

8. Arguments

A. Rejection of claims 1-4, 7-9 and 12-20 under 35 USC § 103(a)

Appellant respectfully submits that the rejection of the identified claims under 35 USC § 103(a) as unpatentable over Nishibe (US 2006/0166953) in view of Saidi et al. (US 6,241,969) and Lintz et al. (US 2004/0247628) is improper and should be reversed.

As a preliminary matter, appellant respectfully notes that claims 1-10 and 12-20 are currently pending and under appeal. However, the Examiner indicated that claim 11 is also rejected as unpatentable under §103(a) over these references. Appellant respectfully notes that presently rejected claim 11 was canceled in the Amendment and Response on January 19, 2011.

Appellant further respectfully notes that no basis for rejecting claim 10 is currently of record. Accordingly, appellant respectfully requests that the Examiner indicate the allowability of presently pending claim 10 in her next communication to appellant.

The state of the law

The U.S. Supreme Court in *Graham v. John Deere Co.*, 148 U.S.P.Q. 459 (1966) held that non-obviousness was determined under 35 USC § 103 by: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the art; and, (4) inquiring as to any objective evidence of non-obviousness.

Furthermore, to establish a *prima facie* case of obviousness, the Examiner must satisfy three requirements. First, as the U.S. Supreme Court held in *KSR International*

Co. v. Teleflex Inc. et al., 550 U.S. 398 (2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*KSR*, at 417). Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Also, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

A *prima facie* case of obviousness must also include a showing of the reasons why it would have been obvious to modify the references to produce the present invention. See *Ex parte Clapp*, 277 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). The Examiner bears the initial burden to provide some convincing line of reasoning as to why the ordinary skilled artisan would have found the claimed invention to have been obvious in light of the reference teachings. *Id.* at 974.

The presently claimed subject matter

Independent claim 1 is directed to "a method for preparing a sterile aqueous suspension of ciclesonide suitable for nebulization comprising the steps of: (a) providing an aqueous suspension of ciclesonide, containing at least one non-ionic agent for adjusting osmolality, and one or more pharmaceutically acceptable excipients, which one or more excipients are all non-ionic excipients; and (b) autoclaving the aqueous suspension provided in (a)."

Independent claim 2 is directed to "a method for preparing a sterile aqueous suspension of ciclesonide suitable for nebulization comprising the steps of: (a) providing an aqueous suspension of ciclesonide, containing at least one non-ionic agent for adjusting osmolality and optionally further one or more pharmaceutically acceptable excipients, which one or more excipients are all non-ionic excipients; and (b) autoclaving the aqueous suspension provided in (a)."

No prima facie case of obviousness has been properly established

Appellant respectfully submits that a *prima facie* case of obviousness has not been established against the presently pending claims because 1) a person of ordinary skill in the art would not combine the divergent teachings of Nishibe et al., Saidi et al. and Lintz et al.; and 2) even if a person of ordinary skill in the art would combine the teachings of these references, she would find no motivation in the cited references to choose only "non-ionic excipients" as presently claimed.

There is no motivation to combine the Nishibe et al., Saidi et al. and Lintz et al. references.

Appellant respectfully submits that a person of ordinary skill in the art would not be motivated to combine the teachings of the Nishibe et al., Saidi et al. and Lintz et al. references to arrive at the presently pending claims.

The presently pending claims, as exemplified by claim 1, are directed to a method for preparing a sterile aqueous suspension of ciclesonide suitable for nebulization comprising the steps of:

a. providing an aqueous suspension of ciclesonide, containing at least one non-ionic agent for adjusting osmolality, and one or more pharmaceutically acceptable excipients, which one or more excipients are all non-ionic excipients; and

b. autoclaving the aqueous suspension provided in (a).

As conceded by the Examiner on page 4 of the Official Action, the suspension that is taught by Nishibe et al. is not suitable for nebulization because it does not contain an agent for adjusting the osmolality of the suspension. Indeed, Nishibe et al. teach at paragraph [0046] that the suspensions can be administered "via any other routes than nasal such as ophthalmic, transdermal or oral route." As such, the compositions of Nishibe et al. are clearly not intended for inhalation or nebulization. Furthermore, Nishibe et al. is silent with regard to the osmolality of the suspensions or the fact that the suspension must be isosmotic to avoid irritation during administration through nebulization.

Further, Nishibe et al. discloses some of the problems associated with autoclaving suspensions. In particular, Nishibe et al. address the issue of "drug content uniformity" in paragraph [0014] and explain that the uniformity

> "of [an] aqueous suspension containing a water-insoluble drug tends to be depressed by autoclaving, even if the drug is chemically stable. Such a phenomenon, the depression of content uniformity, is explained that some particles of water-insoluble drug that are once dissolved or partly dissolved to smaller particles under such high temperature appeared again as various size of particles during subsequent cooling, leading to wider range of particle size distribution in suspension."

Therefore, starting with the Nishibe et al. reference, the person of ordinary skill in the art is faced with the technical problem of providing a sterile aqueous ciclesonide suspension that does not suffer from clogging and a suspension that is suitable for nebulization, i.e. inhalative administration.

The presently claimed method requires that the "sterile aqueous suspension of ciclesonide" is "suitable for nebulization" after autoclaving. The Examiner attempts to remedy the deficient teachings of the Nishibe et al. reference by using the Saidi et al. reference which does discuss nebulization but has absolutely no teaching regarding autoclaving.

Instead, the compositions disclosed in Saidi et al. are all sterilized by use of a 0.22 micron sterile filter and not by autoclaving. Clearly, a reference that does not even teach autoclaving cannot provide the ordinary skilled artisan with the requisite motivation to solve the technical problems associated with autoclaving – namely to provide a sterile aqueous ciclesonide suspension that does not suffer from clogging and a suspension that is suitable for nebulization, i.e. inhalative administration. Indeed, sterilizing the suspension of Nishibe et al. through the filtration method of Saidi et al.

would result in the loss of the ciclesonide in suspension. Thus, one of ordinary skill would certainly not look to the filtration method of Saidi et al. to remedy the deficiencies of the autoclaving method of Nishibe et al.

Further, the compositions of Saidi et al. are "formulated such that they contain the corticosteroid active agent(s) in a dissolved state." *See* col. 5, lines 34-35. Again, appellant notes that the methods of the presently pending claims are directed to preparing ***suspensions*** of ciclesonide sterilized through ***autoclaving*** suitable for nebulization. In contrast, the methods of Saidi et al. are focused on ***solutions*** of corticosteroids sterilized through ***filtration***. One of ordinary skill would not look to a reference teaching a ***solution*** of an active sterilized through ***filtration*** to modify a method of preparing a ***suspension*** of an active sterilized through ***autoclaving***.

Therefore, a person of ordinary skill in the art would not look to the Saidi et al. reference to remedy the deficient teachings of Nishibe et al. to arrive at the presently pending claims.

Similarly, the compositions disclosed in Lintz et al. are also sterilized by use of a 0.22 micron sterile filter and not by autoclaving. As was true with the Saidi et al. reference discussed above, a reference that does not even teach autoclaving cannot provide any motivation to solve the technical problems associated with autoclaving – namely to provide a sterile aqueous ciclesonide suspension that does not suffer from clogging and a suspension that is suitable for nebulization, i.e. inhalative administration. Similar to Saidi et al, sterilizing the suspension of Nishibe et al. through the filtration method of Lintz et al. would result in the loss of the ciclesonide in suspension. One of

ordinary skill would not look to the filtration method of Lintz et al. to remedy the deficiencies of the autoclaving method of Nishibe et al.

Further, the compositions of Lintz et al. contain "a sterile aqueous liquid capable of dissolving the solid composition for said liquid pharmaceutical composition." *See* paragraphs [0012] and [0016] of Lintz et al. Again, appellant notes that the methods of the presently pending claims are directed to preparing ***suspensions*** of ciclesonide sterilized through ***autoclaving*** suitable for nebulization. In contrast, the methods of Lintz et al. are focused on ***dissolving*** the solid composition to form a liquid composition that is sterilized through ***filtration***. One of ordinary skill would not look to a reference teaching a solution of an active sterilized through filtration to modify a method of preparing a suspension of an active sterilized through autoclaving.

Therefore, a person of ordinary skill in the art would not look to the Lintz et al. reference to remedy the deficient teachings of Nishibe et al. and/or Saidi et al. to arrive at the presently pending claims.

Accordingly, it is improper hindsight reconstruction for the Examiner to combine the teachings of the Nishibe et al., Saidi et al. and Lintz et al. references to allege that the presently pending claims are obvious.

In Response to the Examiner's "Response to Arguments" on page 9 of the Official Action, appellant respectfully notes the following. The Examiner has asserted that there is sufficient motivation to combine the cited references by stating:

> "Although the compositions of Nishibe et al. are not administered via inhalation or nebulization, Saidi et al. provides the motivation to make a nebulizer formulation of ciclesonide. Particularly, Saidi et al. teach that composition can be made with corticosteroids to be deliver (sic) through a nebulizer to provide treatment for ailments and diseases of the respiratory tract."

Appellant respectfully disagrees with the Examiner's position and respectfully submits that the Examiner is using improper hindsight to allege her *prima facie* case. The Examiner makes the mere conclusory statement that "Saidi et al. provides the motivation to make a nebulizer formulation of ciclesonide", but offers absolutely no substance to demonstrate how or why the ordinary skilled artisan would be so motivated in view of the clearly deficient teachings of this reference. In particular, the Examiner has failed to address how the ordinary skilled artisan would be motivated to combine the Saidi et al. and Lintz et al. references, which do not even teach autoclaving, with the Nishibe et al. reference which teaches the technical problems associated with autoclaving.

Accordingly, appellant respectfully submits that, other than the Examiner's mere hindsight and conclusory assertion that sufficient motivation exists to combine the diverse teachings of these cited references, no such motivation exists with any reasonable expectation of success as required by *Amgen v. Chugai*, supra.

There is no teaching in the Nishibe et al., Saidi et al. and Lintz et al. references to select only non-ionic agents

Assuming *arguendo* that a person of ordinary skill would look to the combined teachings of Nishibe et al., Saidi et al. and Lintz et al., it is clear that they would find absolutely no teaching within these references to select only the presently claimed "non-ionic" agents to arrive at the presently pending claims.

Appellant respectfully notes that, on page 4 of the Official Action mailed March 11, 2011, the Examiner refers to Saidi et al. at column 7, lines 3-9 and alleges that Saidi

et al. sufficiently teaches the addition of an osmolality agent such as glucose. However, the Examiner essentially ignores that this section of Saidi et al. not only teaches the non-ionic osmolality agent glucose, but also teaches the ionic osmolality agent sodium chloride.

Thus, Saidi et al. teaches the possible addition of an osmotic agent generally with no recognition that the presently claimed non-ionic agents provide a sterile aqueous ciclesonide suspension that does not suffer from clogging and a suspension that is suitable for nebulization, i.e. inhalative administration. Specifically, Saidi et al. teach that "such agents include **any** low molecular weight water-soluble species pharmaceutically approved for pulmonary and nasal delivery such as **sodium chloride** and glucose." (emphasis added).

Further, Example 5 of Saidi et al. actually compares solutions with and without sodium chloride. The results of the study of Example 5 show very little difference between those solutions containing a 0.9% sodium chloride solution and those that do not contain such a 0.9% sodium chloride solution. *See* Example 5 at cols. 12-13 of Saidi et al. Thus, a person of ordinary skill in the art, upon consulting the Saidi et al. reference, would note that ionic agents such as sodium chloride may be perfectly acceptable agents for inclusion in a nebulized formulation.

However, it is clear from a careful reading of the instant specification that ionic osmotic agents such as sodium chloride – indeed even in the same concentration as that disclosed as acceptable in Saidi et al. – do not successfully render the presently claimed "sterile aqueous suspension of ciclesonide suitable for nebulization". In this

regard, appellant respectfully notes that in Example 7 on page 11 of the instant specification, a comparison was made between two formulations:

Formulation I contained 0.05% micronized ciclesonide, 0.025% Polysorbate 20 as suspending agent **and 0.9% sodium chloride**.

Formulation VII contained only 0.05% micronized ciclesonide and 0.025% Polysorbate 20 as suspending agent.

After sterilization of each Formulation, it was shown that the suspension that contained no ionic agent (i.e. sodium chloride) exhibited no significant increase in the particle size. Conversely, the suspension containing the ionic agent rendered "Large white agglomerates". ***Such agglomerates are not suitable for nebulization.*** In this regard, appellant respectfully notes that **MPEP 2143.01** clearly states that, regarding motivation to properly combine or modify references, a proposed modification cannot render the prior art unsatisfactory for its intended purpose. If it does, then there can be no suggestion or motivation to make the proposed modification. See **MPEP 2143.01.**

Clearly, Saidi et al. do not appreciate the significance of using only non-ionic agents for adjusting the osmolality of suspensions containing actives such as ciclesonide. As such, Saidi et al. can be viewed as teaching away from suspensions containing only non-ionic agents for adjusting osmolality. Further, the teaching contained in Saidi et al. regarding the possible acceptability of sodium chloride would render the prior art unsatisfactory for its intended purpose.

In view of the clear lack of teaching or suggestion contained in the cited references regarding the selection of **only** non-ionic agents in the presently claimed method, the presently pending claims are not obvious over the cited references.

In Response to the Examiner's "Response to Arguments" on page 10 of the Official Action, appellant respectfully notes the following. The Examiner has attempted to rebut appellant's position by stating:

> "[o]ne cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller* ...
>
> First, Saidi et al. is used to teach that non-ionic and ionic osmotic agents are known to be used in the art to adjust the osmolality of a composition from about 280-300 mosmol/kg for corticosteroid formulations... Second, example 5 does not use ciclesonide nor compare it with glucose.
>
> Third, one skilled in the art would have the ability and skill to test for the best osmotic agent to render the best result for nebulization based on the teachings of Nishibe et al., Saidi et al., Lintz et al. and Sambuco et al. Selection of a known material based on its suitability for its intended use is obvious."

Appellant respectfully disagrees with the Examiner's various statements.

First, regarding the Examiner's allegation that appellant has attacked the references individually, appellant respectfully disagrees and submits that appellant has simply made the arguments presented as brief and succinct as possible. Therefore, appellant has not simply attacked each reference individually as alleged by the Examiner. Rather, appellant has clearly discussed the teachings of each reference in the context of the teachings of the other references and, as such, has addressed the rejection of the claims as a whole.

Next, regarding the Examiner's seeming assertion that, because example 5 of Saidi et al. does not use ciclesonide nor compare it with glucose, the disclosure contained in example 5 is somehow not probative, appellant wholeheartedly disagrees. Appellant respectfully notes that the probative value of example 5 of Saidi et al. is not at all weakened because it does not use ciclesonide nor compare it with glucose. Rather,

example 5 of Saidi et al. clearly shows that a person of ordinary skill in the art, upon reading Saidi et al., would be motivated to use the ionic agent sodium chloride to adjust the osmolality because of the acceptable results achieved. This fact underscores the clear weakness of the Examiner's reliance on Saidi et al. for its mere general teaching of both ionic and non-ionic osmotic agents in her attempts to establish a *prima facie* case of obviousness against the presently pending claims which are limited to non-ionic excipients.

Finally, regarding the Examiner's statement that "one skilled in the art would have the ability and skill to test for the best osmotic agent to render the best result for nebulization based on the teachings of Nishibe et al., Saidi et al., Lintz et al. and Sambuco et al. Selection of a known material based on its suitability for its intended use is obvious", appellant again disagrees. The Examiner has completely ignored the requirements of MPEP 2143.01 by casting aside appellant's arguments and data contained within their specification that shows that the ionic osmotic excipient sodium chloride as taught by Saidi et al. is unacceptable and would "render the prior art [i.e. Nishibe et al.] unsatisfactory for its intended purpose". Thus, the Examiner's statement that appellant is merely selecting a known material based on its suitability for adjusting osmolality has no merit.

As such, for at least these reasons, claims 1-4, 7-9 and 12-20 are not obvious under 35 U.S.C. §103(a) and appellant respectfully requests that the Board of Patent Appeals and Interferences reverse the present rejection of pending claims 1-4, 7-9 and 12-20.

B. Rejection of claim 5 under 35 USC § 103(a)

Appellant respectfully submits that the rejection of the identified claim under 35 USC § 103(a) as obvious over Nishibe (US 2006/0166953) in view of Saidi et al. (US 6,241,969) and Lintz et al. (US 2004/0247628) and further in view of Allen et al. (J. Allergy Clin. Immunol., Sept. 2003, vol. 112, no. 3, pp. s7-s40) and ACS Registry (Feb. 1995, p. 1) is improper and should be reversed.

Appellant respectfully submits that none of the cited references, alone or in combination, render Appellant's pending claim 5 obvious for at least the following reasons.

The requirements for establishing a *prima facie* case of obviousness are outlined above in section 8A. Further, the Nishibe et al., Saidi et al. and Lintz et al. references are discussed in detail in section 8A. For the sake of brevity, appellant incorporates the discussion of the Nishibe et al., Saidi et al. and Lintz et al. references contained in section 8A herewith.

As shown in section 8A of this Appeal Brief, a *prima facie* case of obviousness has not been established against the presently pending claims because 1) a person of ordinary skill in the art would not combine the teachings of Nishibe et al., Saidi et al. and Lintz et al. with any reasonable expectation of success; and 2) even if a person of ordinary skill in the art would combine the teachings of these references, she would find no motivation in the cited references to choose only "non-ionic excipients" as presently claimed.

In addition to the deficiencies outlined above in section 8A, the Nishibe et al., Saidi et al. and Lintz et al. references further do not teach the ciclesonide derivatives of claim 5.

The Examiner relies on Allen et al. and the ACS registry only to show metabolites of ciclesonide. However, the Allen et al. reference and the ACS Registry do not remedy the deficient teachings of these cited references. Allen et al. and the ACS Registry do not provide the proper motivation to modify a suspension sterilized through autoclaving with the teachings of references directed to solutions of actives sterilized through filtration. Further, Allen et al. and the ACS Registry do not provide any motivation to selected only non-ionic agents to be included in the suspensions of Nishibe et al.

In view of the clear lack of teaching or suggestion contained in the cited references regarding the selection of only non-ionic agents in the presently claimed method, the presently pending claims are not obvious over the cited references.

Therefore, a person of ordinary skill in the art would not look to Allen et al. and the ACS Registry to remedy the deficient teachings of Nishibe et al., Saidi et al. and/or Lintz et al. to arrive at the presently pending claims.

Accordingly, it is improper hindsight reconstruction for the Examiner to combine the teachings of the Nishibe et al., Saidi et al., Lintz et al., Allen et al. and the ACS Registry references to allege that the presently pending claims are obvious.

As such, claim 5 is not obvious under 35 U.S.C. §103(a) and appellant respectfully requests that the Board of Patent Appeals and Interferences reverse the present rejection of pending claim 5.

C. Rejection of claim 6 under 35 USC § 103(a)

Appellant respectfully submits that the rejection of the identified claim under 35 USC § 103(a) as obvious over Nishibe (US 2006/0166953) in view of Saidi et al. (US 6,241,969) and Lintz et al. (US 2004/0247628) and further in view of Sambuco et al. (US 2005/0175546) is improper and should be reversed.

Appellant respectfully submits that none of the cited references, alone or in combination, render Appellant's pending claim 6 obvious for at least the following reasons.

The requirements for establishing a *prima facie* case of obviousness are outlined above in section 8A. Further, the Nishibe et al., Saidi et al. and Lintz et al. references are discussed in detail in section 8A. For the sake of brevity, appellant incorporates the discussion of the Nishibe et al., Saidi et al. and Lintz et al. references contained in section 8A herewith.

As shown in section 8A of this Appeal Brief, a *prima facie* case of obviousness has not been established against the presently pending claims because 1) a person of ordinary skill in the art would not combine the teachings of Nishibe et al., Saidi et al. and Lintz et al. with any reasonable expectation of success; and 2) even if a person of ordinary skill in the art would combine the teachings of these references, she would find no motivation in the cited references to choose only "non-ionic excipients" as presently claimed.

The Examiner is correct in her statement on page 8 of the Official Action that the Nishibe et al., Saidi et al. and Lintz et al. references do not teach the particle size of ciclesonide recited in claim 6. However, as stated above in section 8A, the Nishibe et

al., Saidi et al. and Lintz et al. references do not render claims 1-4, 7-9 and 12-20 obvious. Therefore, the Sambuco et al. reference would have to have some teaching that would cure the deficiencies of the other cited references, which it does not.

In particular, Sambuco et al. does not address any of the technical problems associated with autoclaving - namely to provide a sterile aqueous ciclesonide ***suspension*** that does not suffer from clogging and a suspension that is suitable for ***nebulization***. The only disclosure contained in Sambuco et al. regarding autoclaving is a cursory identification of autoclaving as one of many processes that can be used to manufacture sterile formulations for inhalation. See paragraph [0010] of Sambuco et al.:

> [0010] Various processes can be used to manufacture sterile pharmaceutical formulations for inhalation. For example, the active ingredient can be sterilised by dry heating or irradiation, followed by preparation of the formulation under aseptic conditions, or the formulation can be pre-prepared and sterilised by treatment in an autoclave or by filtration.

Further, Sambuco et al. has no teaching that would motivate the skilled artisan to select only the presently claimed "non-ionic" agents to arrive at the presently pending claims.

Sambuco et al. therefore, has no teaching that would cure the deficiencies of the Nishibe et al., Saidi et al. and Lintz et al. references. Therefore, a person of ordinary skill in the art would not look to Sambuco et al. to remedy the deficient teachings of Nishibe et al., Saidi et al. and/or Lintz et al. to arrive at the presently pending claims.

Accordingly, it is improper hindsight reconstruction for the Examiner to combine the teachings of the Nishibe et al., Saidi et al., Lintz et al., and Sambuco et al. references to allege that the presently pending claims are obvious.

As such, claim 6 is not obvious under 35 U.S.C. §103(a) and appellant respectfully requests that the Board of Patent Appeals and Interferences reverse the present rejection of pending claim 6.

Accordingly, Appellant respectfully requests that the Board of Patent Appeals and Interferences reverse all rejections of claims 1-9 and 12-20 and remand the case to the Examiner to issue a Notice of Allowance of all pending claims 1-10 and 12-20.

If a fee is required for an extension of time under 37 C.F.R. §1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account No. 14-0112.

Respectfully submitted,
THE NATH LAW GROUP

Date: August 8, 2011

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9. Claims Appendix

1. (Previously presented) A method for preparing a sterile aqueous suspension of ciclesonide suitable for nebulization comprising the steps of:

   a. providing an aqueous suspension of ciclesonide, containing at least one non-ionic agent for adjusting osmolality, and one or more pharmaceutically acceptable excipients, which one or more excipients are all non-ionic excipients; and

   b. autoclaving the aqueous suspension provided in (a).

2. (Previously presented) A method for preparing a sterile aqueous suspension of ciclesonide suitable for nebulization comprising the steps of:

   a. providing an aqueous suspension of ciclesonide, containing at least one non-ionic agent for adjusting osmolality and optionally further one or more pharmaceutically acceptable excipients, which one or more excipients are all non-ionic excipients; and

   b. autoclaving the aqueous suspension provided in (a).

3. (Previously presented) The method according to claim 1, wherein ciclesonide is selected from the group consisting of [11β,16α(R)]--16,17-[(cyclohexylmethylene)bis(oxy)]- 11-hydroxy-21-(2-methyl-1-oxopropoxy)-pregna-1,4diene3,20-dione, mixtures of the compounds [11β,16α(S)]-

16,17-[(cyclohexylmethylene)bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxo-propoxy)pregna-1,4-diene-3,20-dione) and [11β,16α(R)]--16,17-[(cyclohexylmethylene)bis(oxy)]- 11-hydroxy-21-(2-methyl-1-oxopropoxy)-pregna-1,4-diene3,20-dione in any desired mixing ratio, and mixtures of the compounds [11β,16α(S)]-16,17-[(cyclohexylmethylene)bis-(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)pregna-1,4-diene-3,20-dione) and [11 β,16α(R)]-16,17-[(cyclohexylmethylene)bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)pregna-1,4-diene-3,20-dione consisting essentially of R epimers.

4. (Previously presented) The method according to claim 1, wherein ciclesonide is selected from the group consisting of ciclesonide, solvates of ciclesonide, physiologically functional derivatives of ciclesonide, solvates of physiologically functional derivatives of ciclesonide and mixtures thereof.

5. (Previously presented) The method according to claim 4, wherein the physiologically functional derivative of ciclesonide is selected from the group consisting of 16α,17-(22R)-cyclohexylmethylenedioxy-11β,21-dihydroxypregna-1,4--diene-3,20-dione, 16α,17-(22S)-cyclohexylmethylenedioxy-11β,21-dihydroxy-pregna-1,4-diene-3,20-dione, and mixtures thereof in any mixing ratio.

6. (Previously presented) The method according to claim 1, wherein the mean particle size of ciclesonide is less than 12μm.

7. (Previously presented) The method according to claim 2, wherein the non-ionic agent for adjusting the osmolality is selected from the group consisting of mannitol, glycerol, glucose, lactose, trehalose, sucrose, propylene glycol, sorbitol, xylitol, polyethylene glycol, ethanol, isopropanol, cyclodextrins, derivatives of cyclodextrins and mixtures thereof.

8. (Previously presented) The method according to claim 7, wherein the agent for adjusting the osmolality is selected from the group consisting of mannitol, glycerol, glucose and mixtures thereof.

9. (Previously presented) The method according to claim 1, wherein the suitable excipients are selected from the group consisting of agents for adjusting osmolality, suspending agents, agents for modifying pH of the suspension, chelating agents, preservatives and mixtures thereof.

10. (Previously presented) The method according to claim 2, wherein the suitable excipients are selected from the group consisting of suspending agents, agents for modifying pH of the suspension, chelating agents, preservatives and mixtures thereof.

11. (Cancelled)

12. (Previously presented) The method according to claim 9, wherein an agent for modifying the pH of the suspension is present as excipients, which is an organic acid selected from the group consisting of citric acid, tartaric acid, lactic acid and mixtures thereof.

13. (Previously presented) The method according to claim 9, wherein the suspending agent is selected from the group consisting of polysorbates, tyloxapol, poloxamers, poloxamines, polyoxyethylene castor oil derivatives, phospholipids, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, methylcellulose, polyvinylpyrrolidone, polyvinylalcohol and mixtures thereof.

14. (Previously presented) The method according to claim 13, wherein the suspending agents are polyoxyethylene sorbitan fatty acid esters.

15. (Previously presented) The method according to claim 1, comprising the steps of

a. dissolving the non-ionic excipients or excipients in water;
b. optionally filtering the solution;
c. homogeneously suspending ciclesonide within the solution and
d. autoclaving the aqueous suspension provided in (c).

16. (Previously presented) The method according to claim 2, comprising the steps of

a. dissolving the non-ionic agent for adjusting the osmolality and optionally other excipients in water;

b. optionally filtering the solution;

c. homogeneously suspending ciclesonide within the solution; and

d. autoclaving the aqueous suspension provided in (c).

17. (Previously presented) The method according to claim 1, wherein autoclaving is carried out at a temperature above 90°C.

18. (Previously presented) The method according to claim 17, wherein autoclaving is carried out at a temperature above 120° C.

19. (Previously presented) The method according to claim 17, wherein autoclaving is carried out at 121°C for at least 15 minutes.

20. (Previously presented) The method according to claim 1, wherein the sterile aqueous suspension of ciclesonide suitable for nebulization has an osmolality in the range of 225- 430 mosmol/kg.

21. (Withdrawn) A sterile aqueous suspension of ciclesonide suitable for nebulization containing one or more pharmaceutically acceptable excipients, which one or more excipients are all non-ionic excipients.

22. (Withdrawn) A sterile aqueous suspension of ciclesonide suitable for nebulization containing at least one non-ionic agent for adjusting osmolality and optionally further pharmaceutically acceptable excipients.

23. (Withdrawn) The sterile aqueous suspension according to claim 21, having an osmolality in the range of 225- 430 mosmol/kg.

24. (Withdrawn) The sterile aqueous suspension according to claim 21, wherein the ciclesonide has a mean particle size of less than 12µm.

25. (Withdrawn) The sterile aqueous suspension according to claim 22, wherein the non-ionic agent for adjusting the osmolality is selected from the group consisting of mannitol, glycerol, glucose, lactose, trehalose, sucrose, propylene glycol, sorbitol, xylitol, polyethylene glycol, ethanol, isopropanol, cyclodextrins, derivatives of cyclodextrins and mixtures thereof.

26. (Withdrawn) The sterile aqueous suspension according to claim 25, wherein the agent for adjusting the osmolality is selected from the group consisting of mannitol, glycerol, glucose and mixtures thereof.

27. (Withdrawn) The sterile aqueous suspension according to claim 21, wherein the suitable excipients are selected from the group consisting of agents for adjusting

osmolality, suspending agents, agents for modifying pH of the suspension, chelating agents, preservatives and mixtures thereof.

28. (Withdrawn) The sterile aqueous suspension according to claim 22, wherein the suitable excipients are selected from the group consisting of suspending agents, agents for modifying pH of the suspension, chelating agents, preservatives and mixtures thereof.

29. (Withdrawn) The sterile aqueous suspension according to claim 22, wherein suitable excipients are non-ionic excipients.

30. (Withdrawn) The sterile aqueous suspension according to claim 27, wherein an agent for modifying the pH of the suspension is present as an excipient which is an organic acid selected from the group consisting of citric acid, tartaric acid, lactic acid and mixtures thereof.

31. (Withdrawn) The sterile aqueous suspension according to claim 27, wherein the suspending agent is selected from the group consisting of polysorbates, tyloxapol, poloxamers, poloxamines, polyoxyethylene castor oil derivatives, phospholipids, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, methylcellulose, polyvinylpyrrolidone, polyvinylalcohol and mixtures thereof.

32. (Withdrawn) The sterile aqueous suspension according to claim 31, wherein the suspending agents are polyoxyethylene sorbitan fatty acid esters.

33. (Withdrawn) An aqueous suspension of ciclesonide for administration by nebulization, wherein the concentration of ciclesonide within the suspension for nebulization is in the range of 0.005% to 0.5% (w/v).

34. (Withdrawn) The aqueous suspension according to claim 21, wherein the ciclesonide has a mean particle size of less than 12µm.

35. (Withdrawn) The aqueous suspension of ciclesonide according to claim 33, which is a sterile suspension.

36. (Withdrawn) The sterile aqueous suspension according to claim 21 for administration by nebulization, wherein the concentration of ciclesonide within the suspension for nebulization is in the range of 0.005% to 0.5% (w/v).

37. (Withdrawn) The sterile aqueous suspension according to claim 21 containing as excipients mannitol and polysorbate or glycerol and polysorbate.

38. (Withdrawn) The sterile aqueous suspension according to claim 37, additionally containing hydrochloric acid or citric acid.

39. (Withdrawn) A method for the prophylaxis or treatment of a clinical condition in a patient for which a glucocorticosteroid is indicated, which comprises administration of a therapeutically effective amount of a sterile aqueous suspension of ciclesonide according to claim 21.

40. (Withdrawn) The method according to claim 39, wherein the clinical condition is asthma the patient is a child and the treatment is a continuous treatment regimen and the sterile aqueous suspension of ciclesonide is administered by nebulization.

41. (Withdrawn) A drug product comprising a sealed container containing a sterile aqueous suspension according to claim 21, and a label indicating administration by nebulization in a continuous treatment regimen.

10. Evidence Appendix

No information is appended under this section.

11. Related Proceedings Appendix

No information is appended under this section.